Challenges in the Development of Transdermal Drug Delivery Systems

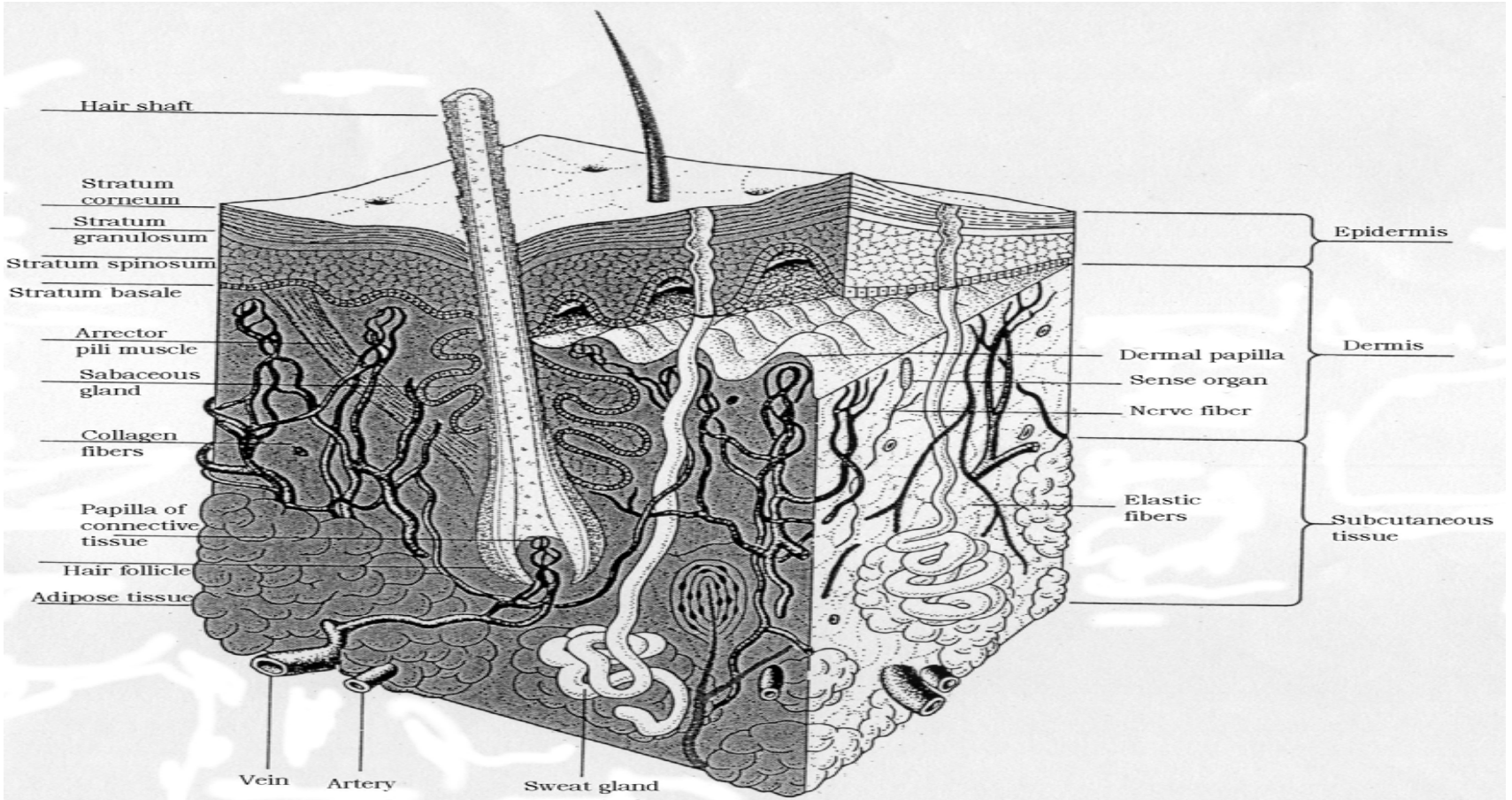
Nakissa Sadrieh, Ph.D.
Associate Director for Research Policy and Implementation
Office of Pharmaceutical Science, CDER, FDA

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

August 5, 2009

What are transdermal drug delivery systems (TDDS) also known as “patches”?

Dosage forms designed to deliver a therapeutically effective amount of drug across a patient’s skin.



Transdermal Drug Delivery Systems (TDDS) have benefits

- Improved patient compliance
- Patients with difficulty in swallowing tablets or capsules
- Avoid irritation of the GI mucosa
- Bypass first-pass inactivation by the liver
- Controlled delivery through the skin can provide less fluctuation in circulating levels of drugs (avoid drug spike levels seen after oral delivery)
- Termination of dosing by removal of TDDS

	DRUG NAME	GENERIC NAME	APPROVAL DATE
RX	CATAPRES TTS	CLONIDINE	October 10, 1984
	FLECTOR	DICLOFENAC EPOLAMINE	January 31, 2007
	VIVELLE	ESTRADIOL	October 28, 1994
	CLIMARA	ESTRADIOL	December 22, 1984
	VIVELLE-DOT	ESTRADIOL	January 8, 1999
	ALORA	ESTRADIOL	December 20, 1996
		ESTRADIOL	February 24, 2000
	MENOSTAR	ESTRADIOL	June 8, 2004
	ESTRADERM	ESTRADIOL	September 10, 1986
	CLIMARA PRO	ESTRADIOL/LEVONORGESTREL	November 21, 2003
	COMBIPATCH	ESTRADIOL; NORETHINDRONE ACETATE	August 7, 1998
	ORTHO EVRA	NORELGESTROMIN/ETHINYL ESTRADIOL	November 20, 2001
	DURAGESIC	FENTANYL	August 7, 1990
		FENTANYL	January 28, 2005
		FENTANYL	August 4, 2006
		FENTANYL	August 20, 2007
		FENTANYL	October 20, 2008
		FENTANYL	August 20, 2007

	DRUG NAME	GENERIC NAME	APPROVAL DATE
RX	LIDOCAINE	LIDOCAINE	May 21, 1996
	SYNERA	LIDOCAINE 70MG/ TETRACAINE 70MG	June 23, 2005
	DAYTRANA	METHYLPHENIDATE	April 6, 2006
	NITRO-DUR	NITROGLYCERIN	April 4, 1995
	MINITRAN	NITROGLYCERIN	August 30, 1996
		NITROGLYCERIN	August 30, 1996
		NITROGLYCERIN	October 30, 1998
		NITROGLYCERIN	August 10, 2004
	ORADISC A	AMLEXANOX	September 29, 2004
	OXYTROL	OXYBUTYNIN	February 26, 2003
	EXELON PATCH	RIVASTIGMINE	July 6, 2007
	TRANSDERM-SCOP	SCOPOLAMINE	Approved prior to January 1, 1982
	EMSAM	SELEGILINE TRANSDERMAL SYSTEM	February 27, 2006
	ANDRODERM	TESTOSTERONE	September 29, 1995

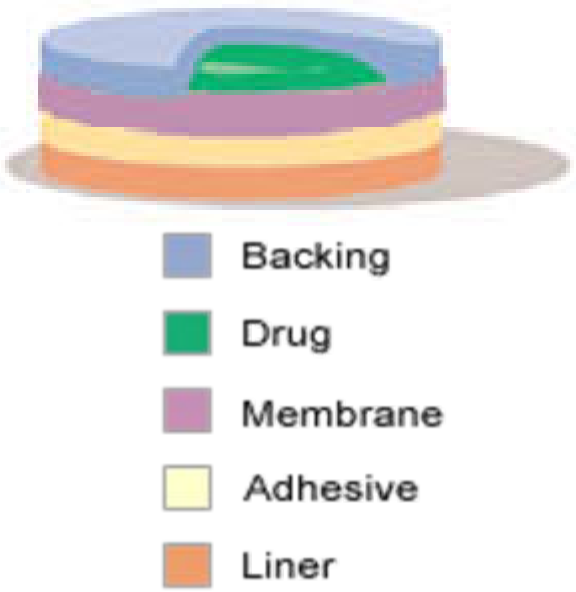
	DRUG NAME	GENERIC NAME	APPROVAL DATE
OTC	NICODERM	NICOTINE	August 2, 1996
	HABITROL	NICOTINE	November 12, 1999
	PROSTEP	NICOTINE	December 23, 1998
	SALONPAS	10 % METHYL SALICYLATE & 3 % MENTHOL	February 20, 2008
DISCONTINUED	LIDOPEL	LIDOCAINE HCL AND EPINEPHRINE	October 26, 2004
	NICOTROL	NICOTINE	July 3, 1996
	TRANSDERM-NITRO	NITROGLYCERIN	February 27, 1996
		NITROGLYCERIN	November 12, 1999
	NEUPRO	ROTIGOTINE PATCH	May 9, 2007
	TESTODERM-AT	TESTOSTERONE	December 18, 1997

Objective

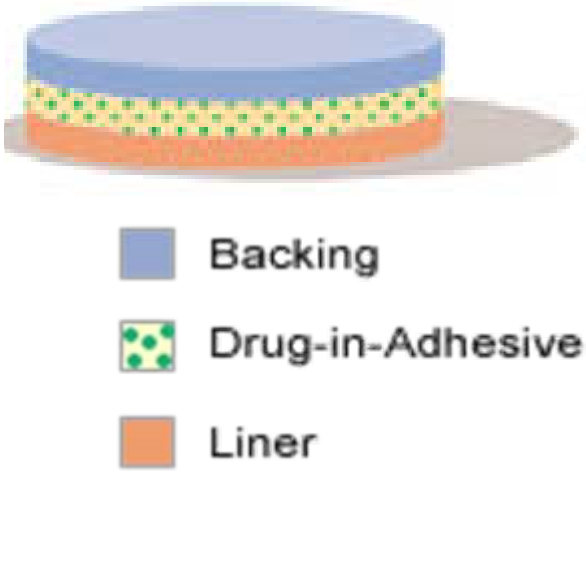
- The agency is considering ways to improve its regulatory oversight of transdermal products.
- Today's discussion is part of a series of activities to help FDA improve its regulatory oversight of transdermal products.
- Future plans:
  - Staff training and workshops to provide CDER with focused input on the scientific issues that can impact performance of transdermal products.

TDDSs have different drug release mechanisms

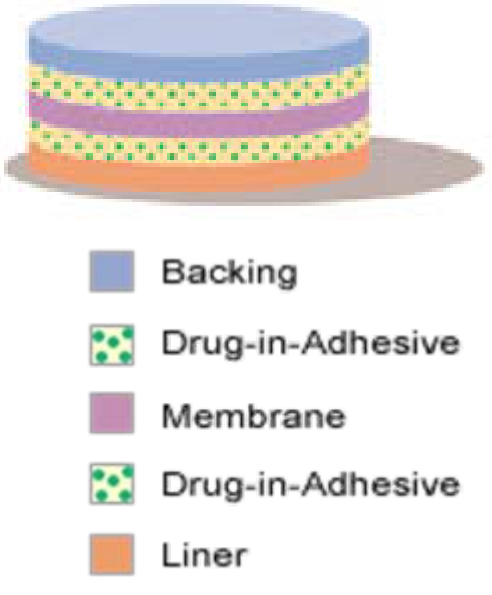
Reservoir system



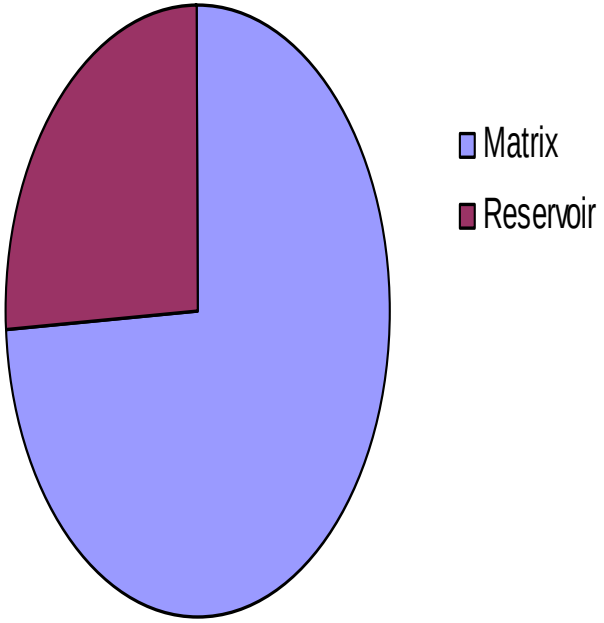
Matrix system without a rate-controlling membrane



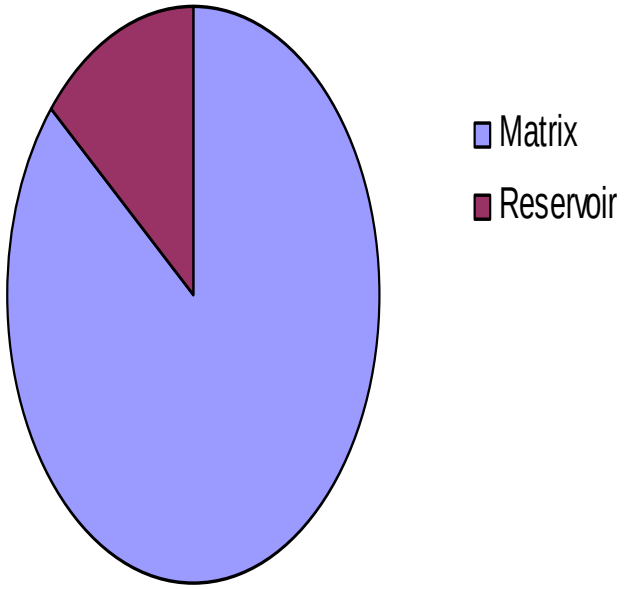
Matrix system with a rate-controlling membrane



Type of Patch (Approved Drugs)



Type of Patch
(Drugs Pending, or under review)

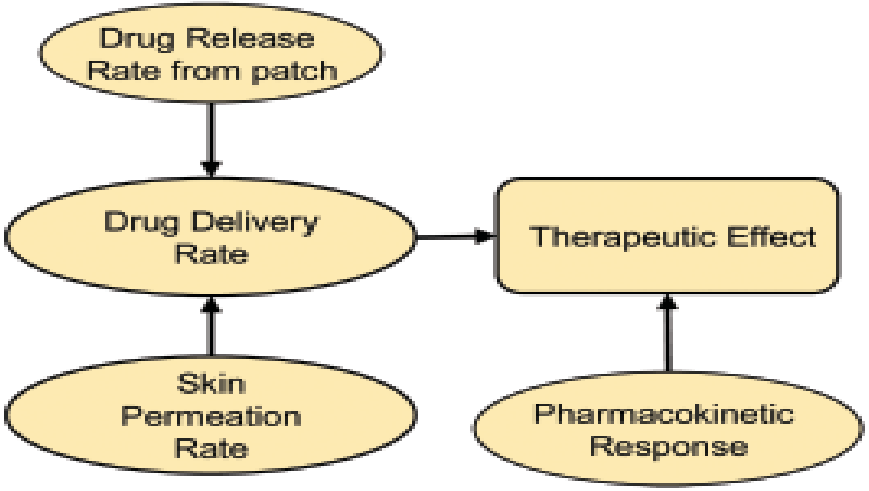


Examples of reports received in FDA's Drug Quality Reporting System (DQRS)

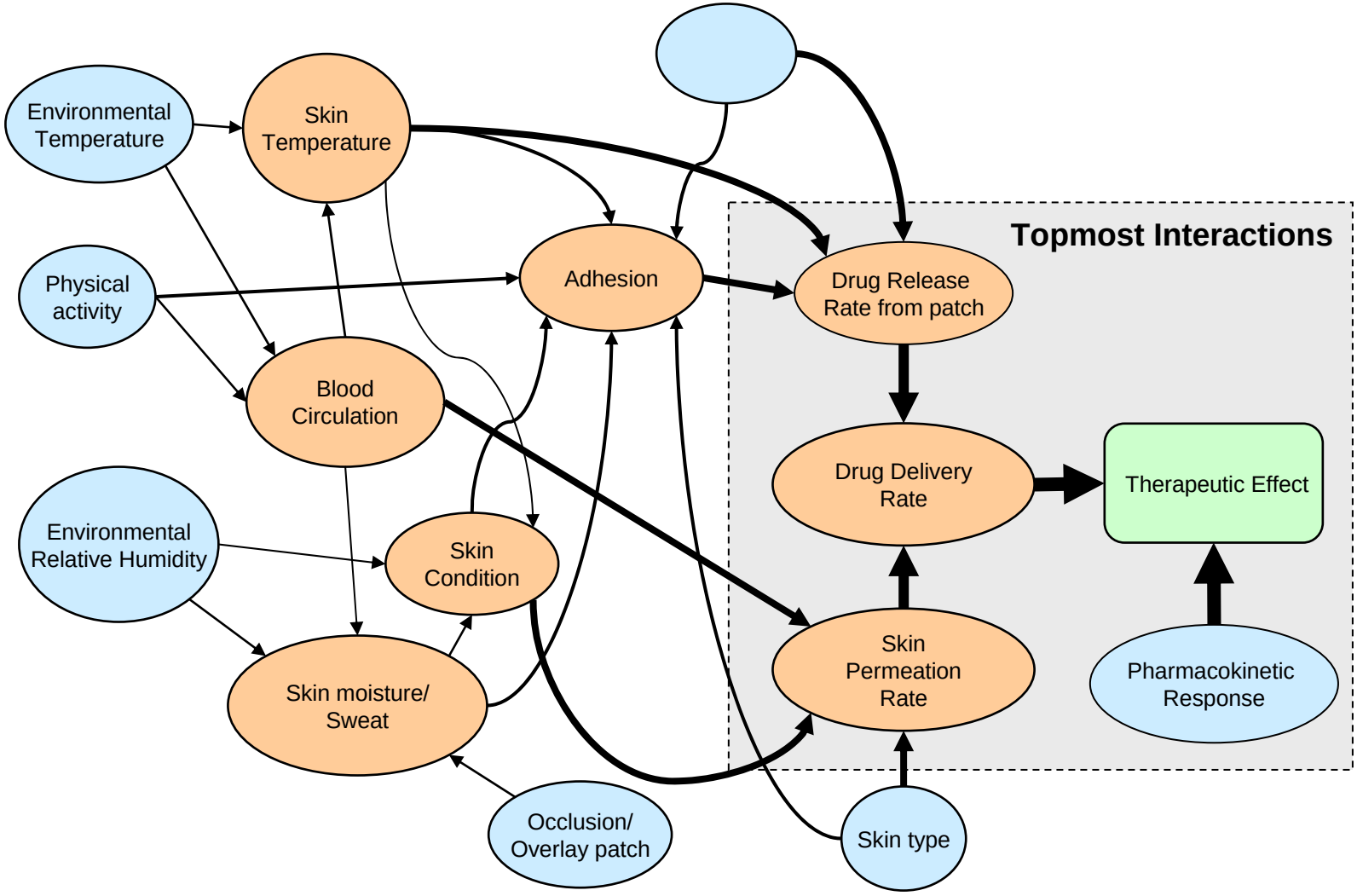
- **Primarily involving lack of adhesion**
  - Environmental condition use failure
    - Heat, cold, sweating, showering, swimming
  - Tape usage in the event of Patch falling off
    - Adhesive from patch not sticking to the skin
    - Complaints about increasing cost to patient, due to lack of adhesion
- **Adverse events at the site of application**
  - Redness, swelling, itching
  - Patch adhered too strongly and removal caused skin tearing, bleeding or inflammation
- **Reports of lack of quality**
  - Release liner cannot be removed properly, either tearing the patch or leaving parts or the entire release liner on the patch, thus making the patch unusable.
  - Patch does not flex or conform to the skin, when skin is moved.
  - Patch not sticking after 24 hours, or edges curling up.
  - Patches coming off in bed (this has been linked to a serious adverse event)
  - Various lots of the same patches looking and "feeling" different.

Development of a risk analysis framework for TDDSs

- Primary variable of interest for TDDS is the therapeutic effect, which is affected by:
  - Drug delivery rate
  - Pharmacokinetic response

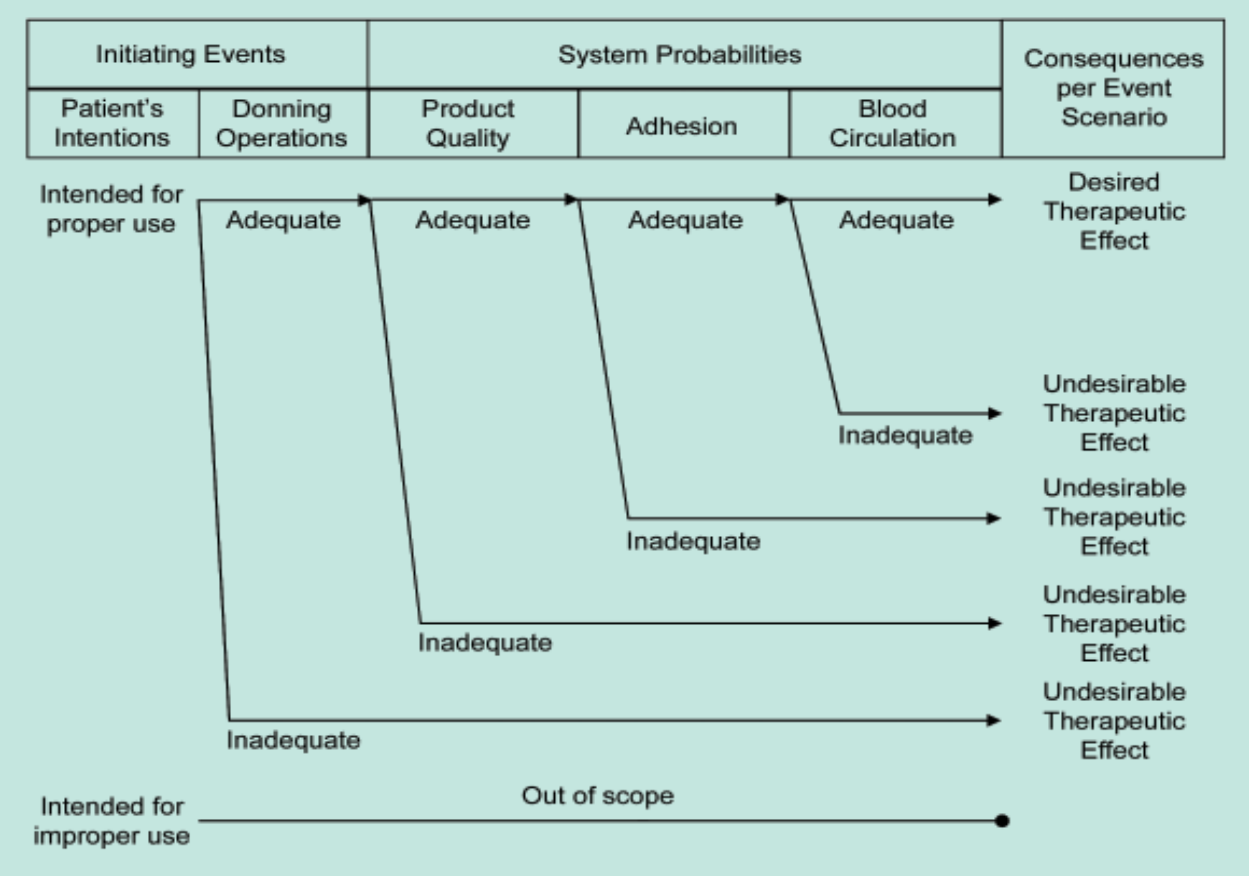


Influence Diagram for TDDS



Event tree

- To systematically identify accident scenarios and quantify risks in situations involving a consecutive group of events.



FDA research on transdermals

- **In vitro drug release:**
  - To develop *in vitro* testing methods for evaluating TDDS performance (drug release and skin permeation studies)
  - To find a suitable synthetic membranes that simulate skin for drug delivery
  - To compare a Matrix and a Reservoir Transdermal Systems in ideal conditions and in the presence of heat and a highly permeable/compromised barrier
  - Evaluate the stability and skin permeation profiles of reservoir systems as a function of patch age
- **In vivo drug release:**
  - Determine the effects of heat (40 C) and occlusion on the pharmacokinetic profile of fentanyl patches in a pig animal model.
- **In vitro adhesive performance:**
  - To develop *in vitro* testing methods to evaluate TDDS adhesion

FDA Publications

1. Evaluating elevated release liner adhesion of a transdermal drug delivery system (TDDS) – A study of Daytrana™ Methylphenidate Transdermal System. Wokovich et al, In preparation.
2. Release liner removal method for transdermal drug delivery systems (TDDSs). Wokovich et al, submitted J. Pharm. Sci.
3. Transdermal Delivery of Fentanyl From Matrix And Reservoir Systems: Effect of Heat and Compromised Skin, Prodduturi et al, submitted J. Pharm. Sci.
4. Reservoir Based Transdermal Drug Delivery Systems: Effect Of Patch Age On Drug Release And Skin Permeation, Prodduturi et al, Pharm. Res., published on line 2009.
5. Evaluation of substrates for 90° peel adhesion- a collaborative study II. transdermal drug delivery systems (TDDS). Wokovich et al, *Journal of Biomedical Materials Research: Part B - Applied Biomaterials* 2009 88B (1), 61-65.
6. Evaluation of substrates for 90° peel adhesion- a collaborative study I. medical tapes. Wokovich et al, *Journal of Biomedical Materials Research: Part B - Applied Biomaterials* 2008 87B(1), 105-113.
7. Risk Analysis of Transdermal Drug Delivery Systems. Kakhi et al. *Pharmaceutical Engineering* 27(4) July/August 2007
8. Transdermal Drug Delivery System (TDDS) adhesion as a critical safety, efficacy and quality attribute. Wokovich et al, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 1-8.

Today's presentations

- Dr. Michniak-Kohn:
  - Design features of transdermal systems
  - Benefits and risks of TDDSs
- Dr. Ravi Harapanhalli:
  - Quality and manufacturing considerations for transdermal systems.

ACPS-CP Questions

Challenges in the Development of Transdermal Drug Delivery Systems (TDDS)

1. What additional measures or next steps should FDA consider to address concerns with the manufacturing and design of transdermal drug delivery systems?